UNIVERSITI PUTRA MALAYSIA

DESIGN, SYNTHESIS, ANTI-INFLAMMATORY ACTIVITY EVALUATION, AND STRUCTUREACTIVITY RELATIONSHIP (SAR) STUDY OF DIARYLPENTANOID DERIVATIVES

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DOCTOR OF PHILOSOPHY
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By

LEONG SZE WEI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

May 2014

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

DESIGN, SYNTHESIS, ANTI-INFLAMMATORY ACTIVITY EVALUATION, AND STRUCTURE-ACTIVITY RELATIONSHIP (SAR) STUDY OF DIARYLPENTANOID DERIVATIVES

By

LEONG SZE WEI

May 2014

Chairman : Associate Professor Faridah Binti Abas, PhD

Institute : Bioscience

Diarylpentanoid is an incredible family of curcuminoid derivatives which had gained increasingly attention recently for its excellent biological importance such as anti-oxidant, anti-inflammatory and anti-cancer activities. 2,6-Bis-(4-hydroxy-3-methoxybenzylidene)cyclohexanone, a diarylpentanoid analog synthesized by our group previously which derived from curcumin with the lack of ethylene unit from the heptane bridge has displayed outstanding anti-inflammatory properties through its inhibition on monocyte chemoattractant protein-1 (MCP-1), interleukin 6 (IL-6), interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF-α) indicates that structural modification on diarylpentanoid could be a promising strategy in discovery of highly potent anti-inflammatory agents.

In this study, one hundred and twenty-five diarylpentenediones and fourteen heterocyclic compounds were synthesized and evaluated for their anti-inflammatory and anti-oxidant activities through cell based nitric oxide assay and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging analysis, respectively. The anti-inflammatory evaluation showed that seventy-three compounds were successfully inhibit nitric oxide (NO) production on IFN-γ/LPS-stimulated RAW264.7 macrophages with the IC_{50} range of 4.18 to 79.87 µM. Among the active candidates, twelve compounds (**9**, **25**, **28**, **63**, **64**, **81**, **83**, **84**, **86**, **88**, **106** and **115**) displayed similar or greater NO inhibitory activity compared to curcumin (14.69 ± 0.240 µM) of which compounds **88** and **106** demonstrated the most significant NO suppression activity with IC_{50} values of 4.89 ± 0.312 and 4.18 ± 0.221 µM , respectively. The structure–activity relationship (SAR) study revealed that the presence of hydroxyl group in both rings is critical for bioactivity of these molecules. Besides, with the exception of polyphenolic derivatives,

low electron density in ring-A and high electron density in ring-B are important for NO inhibition enhancements. Furthermore, pharmacophore mapping showed that hydroxyl groups substituent at both *meta*- and *para*- position of ring-B could be the finger print for highly active diarylpentanoid derivatives.

On the other hand, the anti-oxidant evaluation showed that nine compounds (**83**, **87**, **88**, **89**, **90**, **91**, **92**, **96**, **and 106**) were significantly inhibit DPPH free radical scavenging with 2- to 4-fold better than curcumin (23.56 ± 1.112 μM) of which compound **92** demonstrate the most potent antioxidant activity with the IC_{50} value of 5.58 ± 0.257 μM. Simple SAR study revealed that the remarkable anti-oxidant properties of diarylpentenediones is only depends on the presence of 2',5'- or 3',4'-dihydroxy phenyl rings which indicates the structure skeleton doesn't affect the activity. Therefore, it is conceivably concluded that the diarylpentenediones and their respective heterocyclic derivatives are potent families as anti-inflammatory agents.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

REKA BENTUK, SINTESIS, PENILAIAN AKTIVITI ANTI-RADANG, DAN KAJIAN HUBUNGAN STRUKTUR-AKTIVITI (SAR) BAGI TERBITAN DIARILPENTANOID

Oleh

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Mei 2014

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Diarilpentanoid merupakan kumpulan terbitan luar biasa kurkumin yang telah mendapat perhatian yang semakin bertambah atas kepentingan biologinya seperti anti-oksidaan, anti-radang, dan anti-kanser. 2,6-Bis-(4-hidroksi-3-metoksibenzildiena)sikloheksanon adalah analog diarilpentanoid yang bearasal dari pengubahsuaian struktur kurkumin dengan kekurangan unit etilena dari rantaian heptana telah mempaparkan sifat anti-radang yang hebat melalui kesan perencatannye atas monocyte chemoattractant protein-1 (MCP-1), interleukin 6 (IL-6), interleukin 10 (IL-10) dan tumor nekrosis faktor alfa (TNF-α). Keputusan ini menunjukan bahawa pengubahsuaian struktur diarilpentanoid boleh menjadi strategi yang berpotensi dalam penemuan agen-agen anti-radang yang sangat aktif.

Dalam kajian ini, seratus dua puluh lima analog diarilpentenedion dan empat belas sebatian heterosiklik telah disintesis dan dikaji untuk aktiviti anti-radang dan anti-oksidaan masing-masing melalui perencatan nitrik oksida berasaskan sel dan radikal 2,2-difenil-1-pikrilhidrazil (DPPH). Keputusan penilaian anti-radang menunjukkan bahawa tujuh puluh tiga sebatian telah berjaya menghalang pengeluaran nitrik oksida (NO) pada makrofaj RAW264.7 yang telah dirangsang oleh IFN-γ dan LPS dengan nilai IC_{50} dari 4.18 hingga 79.87 µM. Antara sebatian-sebatian yang aktif, dua belas sebatian (**9**, **25**, **28**, **63**, **64**, **81**, **83**, **84**, **86**, **88**, **106** dan **115**) mempaparkan aktiviti yang lebih baik berbanding dengan kurkumin (14.69 ± 0.240 µM). Antaranya, sebatian **88** dan **106** telah menunjukan aktiviti perencatan NO yang paling signifikan dengan nilai IC_{50} masing-masing ialah 4.89 ± 0.312 dan 4.18 ± 0.221 µM. Kajian hubungan struktur-aktiviti (SAR) mendedahkan bahawa kewujudan kumpulan hidroksil dalam kedua-dua gelang adalah kritikal bagi bioaktiviti molekul-molekul ini. Selain itu, dengan pengeculian terbitan

polifenolik, ketumpatan elektron yang rendah di gelang-A dan ketumpatan elektron yang tinggi di gelang-B adalah penting untuk penambahbaikan aktiviti perencatan NO. Tambahan pula, pemetaan farmakofor menunjukkan bahawa kumpulan hydroksil yang berada pada kedua-dua *meta*- dan *para*- adalah cap jari bagi sebatian yang sangat aktif.

Sebaliknya, keputusan penilaian anti-oksidaan menunjukkan bahawa sembilan sebatian (**83**, **87**, **88**, **89**, **90**, **91**, **92**, **96**, dan **106**) merencat radikal DPPH dengan dua hingga empat kali ganda lebih baik daripada kurkumin (23.56 ± 1.112 µM). Antaranya, sebatian **92** telah mempamerkan aktiviti anti-oksidaan yang paling tinggi dengan nilai IC_{50} 5.58 ± 0.257 µM. Kajian SAR mendedahkan bahawa sifat anti-oksidaan diarilpentenedion yang luar biasa hanya bergantung kepada kehadiran gelang fenil yang mengandungi kumpulan 2',5'-dihydroksi atau 3',4'-dihydroksi. Pemerhatian ini menunjukkan bahawa rangka struktur sebatian tidak menjejaskan aktiviti anti-oksidaan. Oleh itu, diarilpentedion dan sebatian heterosiklik yang telah dihasilkan adalah khusus sebagai agen anti-radang.

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I certify that a Thesis Examination Committee has met on 2014 to conduct the final examination of Leong Sze Wei on his thesis entitled "Design, Synthesis, Anti-inflammatory Activity Evaluation, and Structure-activity Relationship (SAR) Study of Diarylpentanoid Derivatives" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded Doctor of Philosophy.

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Signature: _____	Signature: _____
Name of Member of Supervisory Committee: Syahida Binti Ahmad	Name of Member of Supervisory Committee Md. Nordin Hj. Lajis

Signature: _____
Name of Member of Supervisory Committee: Khozirah Binti Shaari

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

AB	Aerobic biodegradability
ADMET	Absorption, distribution, metabolism, excretion, and toxicity prediction
AlogP	Estimated lipophilicity
AM	Ames mutagenicity
AS	Aqueous solubility
ATCC	American Type Culture Collection
β	Beta
B_2O_3	Boron trioxide
BBB	Blood brain barrier
BBr_3	Boron tribromide
br	Broad
^{13}C	Carbon-13
CADD	Computer aided drug design
CaMKII	Calcium/calmodulin dependent protein kinase II
CHARMm	Chemistry at HARvard Macromolecular Mechanics

CH_2Cl_2	Dichloromethane
Chemical shift	δ
CO_2	Carbon dioxide
CoMFA	Comparative molecular field analysis
COX-2	Cyclooxygenase-2
CYP2D6	Cytochrome P450 2D6
^oC	Degree in Celsius
d	Doublet
dd	Doublet of doublets
DIMS	Direct infusion mass spectrometry
DMEM	Dulbecco's Modified Eagle's Medium
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
DU-145	Prostate cancer cell line
EAC	Ehrlich ascites carcinoma
EtOAc	Ethyl acetate
eNOS	Endothelial nitric oxide synthase
FBS	Fetal bovine serum
g	Gram

GC-MS	Gas Chromatography- Mass Spectrometry
GFA	Genetic function approximation
H_2O	Water
H_2SO_4	Sulfuric acid
HCl	Hydrochloric acid
^1H	Proton
HIA	Human intestinal absorption
HMBC	Heteronuclear Multiple-bond Correlation spectroscopy
HSQC	Heteronuclear Single-quantum Correlation spectroscopy
HT	Hepatotoxicity
Hz	Hertz
IC	Inhibition concentration
IL-1	Interleukin-1
IL-6	Interleukin-6
IFN-γ	Interferon gamma
iNOS	Inducible nitric oxide synthase
J	Coupling constant in Hz

KOH	Potassium hydroxide
LPS	Lipopolysaccharide
MCF-7	Estrogen positive breast cancer cell line
MDA-MD-231	Estrogen negative breast cancer cell line
MFPSA	Molecular fractional polar surface area
m.p.	Melting point
MeOH	Methanol
µg	Microgram
µL	Microliter
mg	Milligram
mL	Milliliter
mm	Millimeter
mmol	Millimolar
mol	Molar
MMPs	Matrix metalloproteinases
Molt 4/C8	Human cancer cell line
MS	Mass Spectroscopy
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl

	tetrazolium bromide
NF-κB	Nuclear factor kappa beta
ng	Nanogram
nm	Nanometer
NMR	Nuclear Magnetic Resonance
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
$POCl_3$	Phosphoryl chloride
PGs	Prostaglandins
pIC_{50}	-log IC_{50}
PPB	Plasma protein binding
ppm	Part per million
q^2	Cross-validation correlation coefficient
QSAR	Quantitative Structure–activity Relationship
r^2	Conventional non-cross validation coefficient
RAW264.7	Murine monocyte-macrophage cell line

RNS	Reactive nitrogen species
RT	Room temperature
RT-PCR	Real-time polymerase chain reaction
s	Second
SF268	Human glioblastoma cell line
SKBr-3	Human breast cancer cell line
TLC	Thin layer chromatography
TNF-α	Tumor necrosis factor Alpha
TOPKAT	Toxicity Prediction by Komputer Assisted Technology
t	Time
UV	Ultraviolet

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Medicinal chemistry is one of the most rapidly developing scientific fields which had integrated both disciplines of chemistry and pharmacology. The main objective of medicinal chemistry is to design and discover new pharmaceutical drugs through synthetic and natural product chemistry with the aids of various pharmacological assays. Early stage of medicinal chemistry was only focused on isolations of bioactive candidates from medicinal plants while the synthesis of natural products was often overlooked meanwhile the discovery of novel pharmaceutical drug was only depended on slow motion serendipity(Gualtieri, 2000). However, after years of evolution, synthetic chemistry is successfully taken over the dominant role of natural product isolation in medicinal chemistry development due its excellent efficiency. The integration of traditional medicinal chemistry and modern computational works such as quantitative structure ±activity relationship (QSAR), molecular docking, and pharmacophore modeling further push current medicinal chemistry to higher realm in drug discovery(Lombardino and Lowe, 2004).

1.2 Curcumin

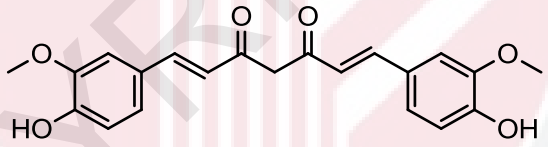
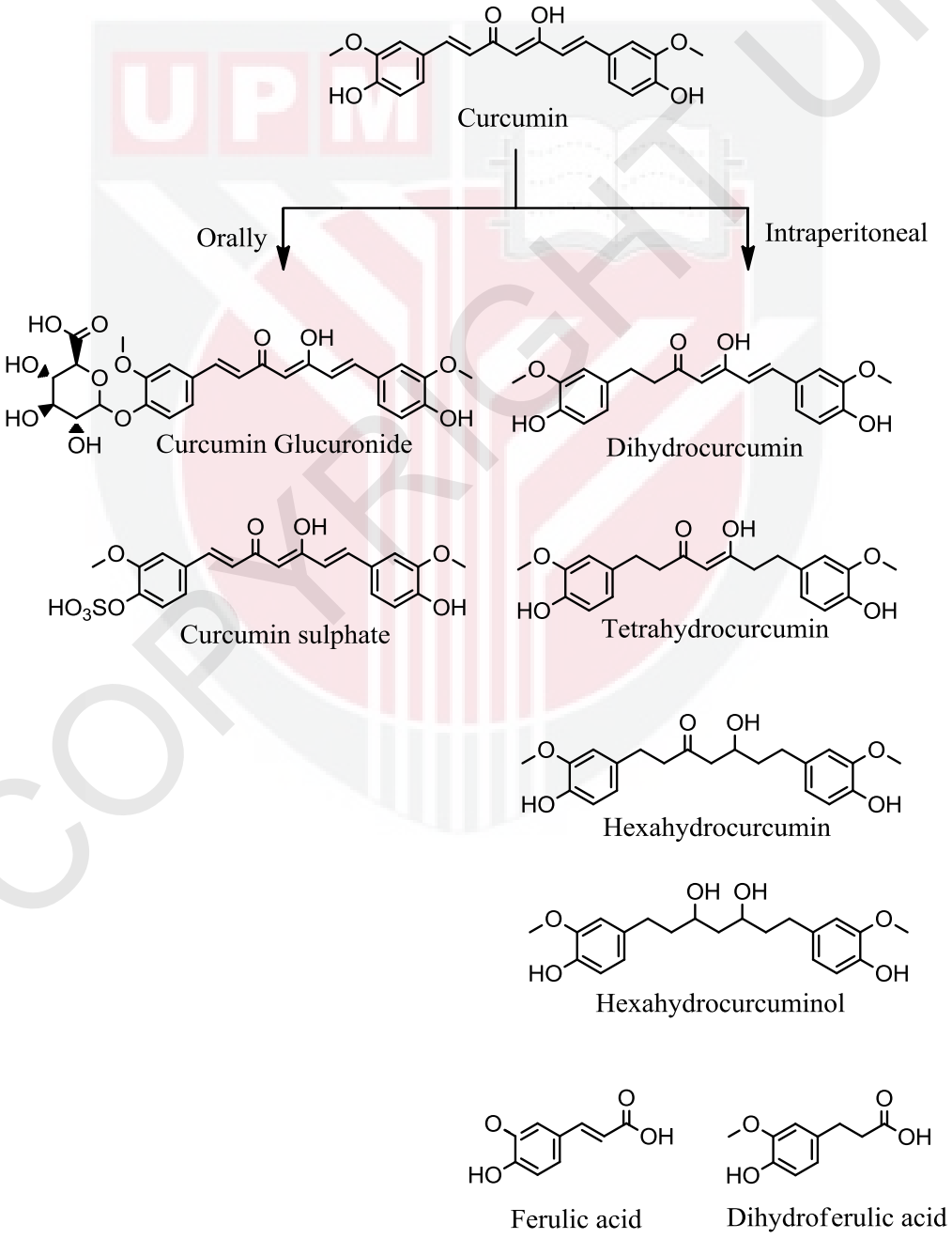


Figure 1. Structure of curcumin
(IUPAC ID: (1E,6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione)

Curcumin (Figure 1) is one of the most famous natural products which had been extensively observed in pass centuries. It is a well-known chemical constituent found in turmeric, an ordinary herb used as Indian curry spice. Curcumin was first isolated from turmeric, *Curcuma longa* in 1815. It can also be found in other plants like *Curcuma mangga*, *Curcuma zedoaria*, *Costus speciosus*, *Curcuma xanthorrhiza*, *Curcuma aromatica*, *Cucruma phaeocaulis*, *Etlingera elatior*, and *Zingiber cassumunar* (Aggarwal et al., 2007). Curcumin exhibits multiple medicinal properties such as antioxidant (Naik et al., 2011b), anti-mutagenic (Gupta et al., 2012), antibacterial (Wang et al., 2009), anti-malarial (Reddy et al., 2005), anti-carcinogen (Limtrakul et al., 1997), anti-angiogenic (Gururaj et al., 2002) and anti-inflammatory (Bisht et al., 2010). The broad biological activities spectrum and extremely mild side effects of curcumin allow it to be widely used in traditional diseases preventions and treatments.

Curcumin had showed its anti-inflammatory potency by suppressing the activation and production of nuclear factor kB (NF- % F \ F O R R [- 2 J (H O X - 2) , and 5-lipoxygenase (5-LOX) and other proinflammatory cytokines such as tumor necrosis factor alpha (TNF- . L Q W H U O H X N L Q , and interleukin-6 (IL-6) (Maheshwari et al., 2006). One of the major drawbacks for the practical use of curcumin is its low absorbability and stability. 7 K H U D S L G P H W D E R O L V P Y L D E W K H β-diketone moiety in the liver and poor solubility are the main causes responsible for low bioavailability of curcumin (Anand et al., 2007). Scheme 1 represents metabolism of bioactive curcumin to non-bioactive ferulic acid and dihydroferulic acid in human body.

Scheme 1. Metabolism of curcumin in human body



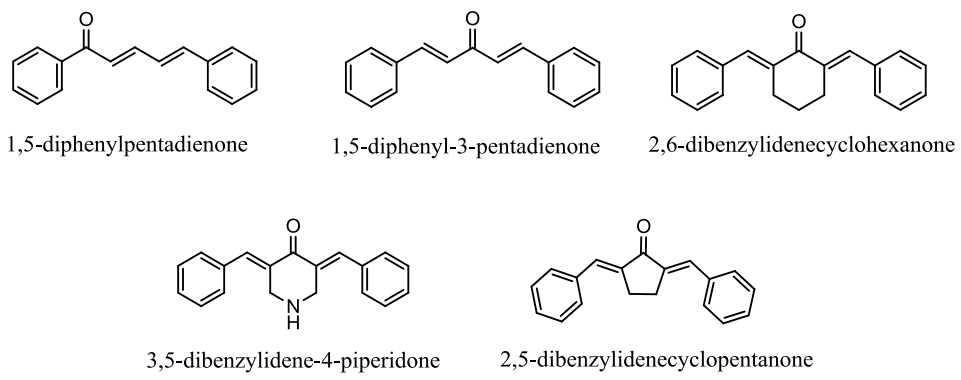
Several strategies have been developed to improve the bioavailability of curcumin including cyclodextrins-complexes (Yadav et al., 2010), nanoparticles-encapsulation (Mulik et al., 2010), piperine supplementation (Banji et al., 2013), chemical structure modifications (Agrawal and Mishra, 2010) and liposomal formulations (Anand et al., 2007). These approaches provide longer circulation, better solubility and cellular permeability as well as induce resistance to metabolic processes in human body which eventually lead to better bioavailability.

Among these strategies, structural modification is the most common method used by current researchers in dealing with poor bioavailability of curcumin and the results obtained suggested that the diarylpentanoid family which contains both methylene protecting group and mono carbonyl moiety is the best design for preserving curcumin-like anti-inflammatory behavior (Weber et al., 2006). Besides, the presence of methylene protecting group could be an important enhancing feature in the sense of bioavailability due to its higher resultant rigidity.

1.3 Diarylpentanoid

Diarylpentanoid is a class of compounds which may be considered as an analogue of curcumin derived from curcumin structure by the lack of ethylene unit from the heptane bridge. In fact, diarylpentanoid has been reported from *Curcuma domestica* at year 1993 and shown to display strong antioxidant activity (Masuda et al., 1993). In recent years, they have gained increasing attention for their excellent pharmacological activities such as anti-inflammatory and antioxidant activities (Lam et al., 2012; Lee et al., 2009; Tham et al., 2010) which eventually caused them to be incredible active in inhibiting numerous chronic diseases such as diabetics (Du et al., 2006b), neurodegenerative diseases (Maher et al., 2010; Narlawar et al., 2007), cancers (Adams et al., 2004; Katsori et al., 2011) and sepsis (Tham et al., 2011). Besides, diarylpentanoid system was also proved to be a potential candidate as whitening agents and pain killer due to their anti-tyrosinase and antinociceptive activities (Hosoya et al., 2012; Ming-Tatt et al., 2012). Therefore, diarylpentanoid system is a promising candidate in developing highly potent multifunctional drugs. Figure 2 depicted general structure of some diarylpentanoid systems which have been studied by recent researches on antioxidant, anti-inflammatory, anti-proliferation, and anti tyrosinase properties (Katsori et al., 2011; Lam et al., 2012; Lee et al., 2009).

Figure 2. General structure of diarylpentanoid derivatives



1.4 Inflammation

Inflammation is a complicated biological protective response which involved numerous proinflammatory cytokines and inflammatory mediators such as nitric oxide (NO) (Korhonen et al., 2005), interleukin (IL-6) (Scheller et al., 2011), prostaglandins (PGs) (Miller, 2006), and tumor necrosis factor-alpha (TNF- . (Rouhani et al., 2005) that are released by various activated leukocytes including polymorphonuclear neutrophils, mast cells, dendritic cells, macrophages, endothelial cells, hepatocytes, B-cells, T-cells and natural killer (NK) cells in response to tissue injury caused by invaded injurious pathogens such as bacterial and viruses (Galley and Webster, 1996). Figure 3 represents the general inflammation scheme described by Karin et al. in 2006 (Karin et al., 2006).

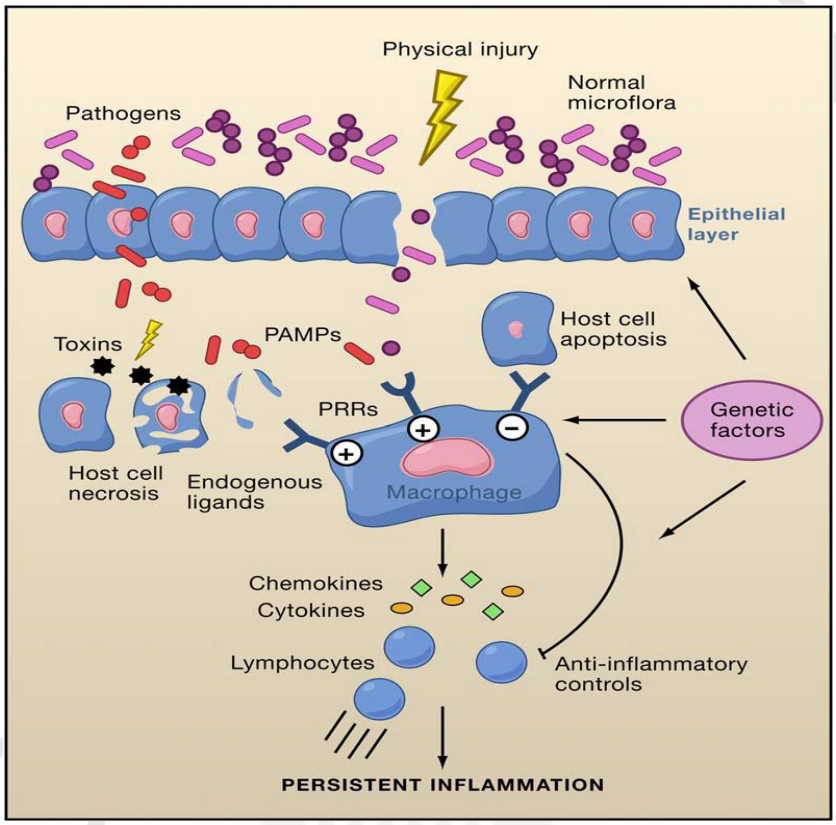


Figure 3. General inflammation scheme (Taken and adapted from Karin et al. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 2006:124:823-835)

As depicted in Figure 3, inflammation is trigger by the infections of invading pathogens such as bacteria and viruses caused by the physical injury. The invaded injurious pathogens interact with body cells and release various toxins which might cause severe cell damages such as cell necrosis and cell apoptosis.

In the early innate immune responses, these invaded pathogens are first attacked by the pioneer fighter of innate immune system, the local immune cells (mainly macrophages) which react spontaneously (phagocytosis) upon foreign substances detection in their territory (Fujiwara and Kobayashi, 2005). During the combat between foreign substances and local immune cells, the fighting phagocytes and

damaged cells will release important chemicals such as histamines (Amin, 2012), prostaglandins (Shen et al., 2008), and leukotrienes (Mandhane et al., 2011) to attract more rescue forces like neutrophils, dendritic cells and macrophages from the blood to the site of inflammation by a series of processes in the sequence of vasolidatioin (increments in arteries and arterioles diameter that allow more blood flow), margination (accumulation and adhesion of phagocytes on blood vessel walls) and emigration (escape of phagocytes through intact vessel walls) where neutrophils, dendritic cells and macrophages are acting as eater cells which engulf the foreign substances through phagocytosis (Colditz, 1985).

At the same time, macrophages and dendritic cells act as antigen presenting cells, the messengers in innate immune system that interact with invaded stimuli and present their information to specific or non-specific immune cells such as neutrophils and lymphocytes in the form of chemokines and cytokines depends on types of invasion (Betjes et al., 1993). The activated neutrophils approach and destroy invaders either through phagocytosis or oxidative burst production where oxidative burst is a faster removing mechanism compared to phagocytosis. In the case of lymphocytes, viruses and bacterial are destroyed by B-cells, T-cells, and natural killer (NK) cells either through the assistance of antibodies produced by B-cells or cytotoxic mechanism exhibit by T-cells and natural killer cells (Galley and Webster, 1996). This immune response cycle will keep going until all foreign substances are eliminated from the organism. After all of the invaded pathogens have been removed, wound healing or tissue repairing process begins to take place. In this final step of inflammation, white blood cells leave the inflammation site to blood stream while resultant dead cells were removed by phagocytes through phagocytosis. At the same time, fibroblasts turn up and begin to repair the damage site with the supports of nutrients and oxygen in vasodilation (Hinz, 2007).

In normal circumstances, inflammation process will be fully stopped once tissue healing was done. However the possibility of prolonged or persistent inflammation does exist when abnormal conditions occurred. These abnormalities always linked to two pivotal factors, the proinflammatory cytokines and inflammatory mediators. Appropriate level of proinflammatory cytokines and inflammatory mediators released are responsible for immune defenses against the invading stimuli but excessive production of such kind cause oxidative damage on cellular components and eventually lead to healthy tissue destruction (Birkedal-Hansen, 1993). Therefore inflammation is a double-edged sword which must be regulated at optimal level in every disease treatment or prevention.

Nitric oxide (NO) is the key molecular signaling constituent involved in inflammatory process. It is biosynthesized endogenously from L-arginine, oxygen and NADPH catalyzed by various nitric oxide synthase (NOS) enzymes. Three major isoforms of NOS found in mammals are neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) (Stuehr, 1999). In chronic inflammation, the presence of lipopolysaccharide (LPS) or other proinflammatory cytokines activate macrophages and induced high level of NO production by iNOS induction. Elevated level of NO production may promote tissue injuries through peroxidation of cell lipids and Deoxyribonucleic acid (DNA) mutation (Routledge, 2000). Besides, it may also aggressively accelerates the formation of peroxynitrite ($NOOO^-$) and peroxynitrous acid (NOOOH), members of reactive nitrogen species (RNS) and cell

destructive agents through the interaction of NO and superoxide (Beckman et al., 1990). The resulting peroxynitrite will then induce the production of destructive carbonate radical ($^{\bullet}OCO_2^-$) by homolysis of peroxynitrosocarbonate ($NOOOCO_2^-$), an extremely reactive species produced by the coupling of peroxynitrite and carbon dioxide (Trujillo et al., 2005). Therefore, overproduction of NO is one of the most important factors contributes to various chronic degenerative diseases including cancer, (Ridnour et al., 2008) cardiovascular disorder (Naseem, 2005), asthma (Fitzpatrick et al., 2009), arthritis, neurodegenerative diseases (Hensley et al., 1997), multiple sclerosis (Sellebjerg et al., 2002), X O F H U D W L Y H F R O L W L V D Q G (Marnett, 2012). Hence, pharmacological interference with NO production is a promising strategy in developing potent drugs for chronic diseases. Lornoxicam , piroxicam, indomethacin and diclofenac are some examples of common analgesic NSAIDs used in arthritis treatments which possess strong anti-inflammatory properties due to their inhibitory effect on various pro-inflammatory enzymes including cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and Inducible nitric oxide synthase (iNOS)(Berg et al., 1999).

1.5 Problem Statements

The usefulness of current NSAIDs was limited due to their undesired adverse side effects including heart failure, gastrointestinal ulceration and bleeding, renal hypertension and edema, as well as platelet dysfunction and cognitive dysfunction (Graham et al., 1988; Rainsford, 1999; Singh and Triadafilopoulos, 1999). The discovery of new NSAIDs with reduced side effect therefore is a must in drugs discovery today. Curcumin is a potent candidate as new NSAID based on its superior anti-inflammatory activity and extremely low toxicity. However the utilization of F X U F X P L Q ¶ V P H G L F L Q D O S U R S H U W L H V L Q F O L Q L F D O bioavailability. Recent reports showed that current structural modifications of diarylpentanoid derivatives were only restricted on mono carbonyl analogues. To the best of our knowledge, none R I W K H V W X G L H V L Q Y H V W L J D W H W K H H in diarylpentanoid system on their biological activities. Therefore, we preserved the -diketone moiety in designing novel diarylpentanoid system in this study which provides additional hydrogen-bond donors or acceptors that might improve the ligand-receptor interactions of diarylpentanoid system with inflammatory-related receptors and hence better inhibitory performance. In addition, we have designed a new series of novel diarylpentanoid derivatives by introducing cyclohexyl ring into W K H V D P H V \ V W H P Z K L F K F R X O G L Q F U H D V H F R P S R X Q G V rigidity achieved (Veber et al., 2002). The general structures of targeted compounds are shown in Figure 4.

1,5-diphenyl-1,3-pentenedione

2-benzoyl-6-benzylidenecyclohexanone

Figure 4. Structures of targeted compounds

All synthesized compounds were evaluated with their anti-inflammatory and antioxidant properties.

1.6 Objectives of this study

1. To design and synthesize novel diarylpentanoid derivatives as new anti-inflammatory agents.
2. To evaluate antioxidant and anti-inflammatory activity of synthesized diarylpentanoid derivatives through DPPH free radical scavenging and nitric oxide inhibitory assays, respectively.
3. To predict bioactive molecular fragments of diarylpentanoid derivatives through quantitative structure ±activity relationship (QSAR) and pharmacophore mapping.
4. To predict the bioavailability and toxicities of selected compounds by using ADMET and TOPKAT analysis.

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